different outcome than did the not heavier patient?

DR. SABLE: Weight was one of the covariates which we looked at in the population pharmacokinetics studies, and although what you point out, Dr. Fletcher, is correct, that there are patients who have higher and more variable levels who are light weight, when you look in comparison of those to average weight of approximately 60 to 70 kilos and then look at patients who have higher weights, there was not as much of a difference at the high end. So more of the difference was at the lower end.

And the fact is if you try to adjust for mean body weight at the low end, what you end up doing is you could potentially under dose some of the patients.

We don't have a lot of data at the higher end, but we have not seen any of the association there with outcomes and weight in those individuals.

DR. FLETCHER: Let me move to drug interactions for a moment. You have pharmacokinetic data, for example, on amphotericin and itraconazole with no PK interaction. I'm wondering, however, is there any reason to think that there could be a mechanistic antagonism between amphotericin and caspofungin or itraconazole. So something separate

from pharmacokinetics, for example, a mechanistic.

DR. SABLE: If your question is regarding the combination of the two drugs together and not just pharmacokinetics, we have actually looked at the combinations of caspofungin with itraconazole combination with fluconazole and amphotericin, also in preclinical studies to look in vitro and in vivo for evidence of whether or not you would have potentially synergy additive effects, indifferent effects or antagonism.

And in those studies we have not seen any evidence of antagonism when they're put together, and we wouldn't expect that there would because of the differences in mechanisms of action.

DR. FLETCHER: This is almost maybe more of a comment than a question. You've noted the potential interaction going on between cyclosporin and caspofungin and with the recommendation that the drugs not be used together, but clearly if this compound is approved, the drugs most likely will be used together.

So I'm not sure what the intent of the agency or the sponsor is, you know, in product information, but it would seem to me while the recommendation is probably reasonable, that the information that you know about those two drugs being

given together does need to be communicated in some fashion.

DR. SABLE: And to respond to your question regarding cyclosporin and caspofungin and the interaction and recommendations for use or not, we'll certainly work closely with the agency about the wording, and as I mentioned, the data that we saw in the Phase I study were mild elevations to two to three times the upper limit of normal that went away when both drugs were stopped. Because they were healthy subjects and it occurred after one day of dosing, we didn't really feel we could explore that further in healthy subjects.

We are now trying to within the context of the salvage aspergillus study, patients who have really limited options, to be able to try to get some additional information, and we have the one patient who showed no elevations over nine days.

We think that in that type of setting where actually we could make a risk benefit we should get at least some information to see whether the observations we've seen in this individual patient are representative before we would actually go on to formally try to dose the two drugs together.

But we agree that cyclosporin is one of

the common immunosuppressants that we do need to investigate that, and we're trying to gather information in settings where we think we can justify risk-benefit to do that.

DR. FLETCHER: Lastly, on drug interactions, tacrolimus, you show that the concentrations of this drug are reduced about 25 percent. First I'm wondering if you have any idea what the mechanism of that interaction might be.

DR. SABLE: I'm sorry. I didn't hear.

DR. FLETCHER: What the mechanism of the interaction might be between caspofungin and tacrolimus, that the tacrolimus levels are reduced about 25 percent.

DR. SABLE: Can I please ask Dr. Stone from our Clinical Drug Metabolism Group to answer that?

DR. STONE: Yes, this is Julie Stone from Drug Metabolism at Merck.

Actually it's not clear what that mechanism of the interaction is. It can't be an induction of 3A4 because we haven't seen similar reductions with cyclosporin or itraconazole when they were co-administered, but beyond that we don't have any clear evidence what that mechanism is.

DR. FLETCHER: Maybe you want to stay up here a while.

(Laughter.)

DR. FLETCHER: You talk about inducers, that you provide information that caspofungin is not a substrate for CIP (phonetic), but then have a proposed recommendation that it not be given with inducers of drug metabolism. So that seems, you know, inconsistent that you could have a compound that's not a substrate, but worried about a lower drug concentration if you give it with an inducer of CIPs. I wonder if you could say something about that.

DR. STONE: Sure. I think, first, to just clarify, we actually have some additional data on the effect of inducers that's come in post submission for some preliminary results of two Phase I interaction studies that were conducted. They've been submitted to the agency, but they haven't had a chance to review these, but they suggest that the finding we saw with nelfinavir in the population PK wasn't a real finding. When we tried to reproduce this in a Phase I study, we see no meaningful effect.

On the other hand, we've also looked at rifampin, and what we seem to see is both an inhibition effect and an induction effect on

caspofungin disposition. The timing and the nature of these effects lead us to believe that it's probably acting at the level of active transport, and I think it's pretty well recognized that rifampin induces pretty broadly, and it's even been demonstrated to induce PGP, a transporter.

So I think it's not unreasonable to think that some of these inducers could also be impacting active transport.

DR. FLETCHER: Thank you.

Resistance. You mentioned in the presentation that resistance is rare, but unless I missed, I didn't see any data on resistance. So in, for example, your 019 study, do you have data, you know, on the issue of resistance? Did patients develop resistance to this drug?

DR. SABLE: In talking about resistance and filamentous fungi, resistance in that setting is very difficult, and that's where the work that's been done has been done with candida.

One of the difficulties in talking about resistance as far as in vitro susceptibility is that that really kind of denotes outcome, and at this point there is not standardized susceptibility testing methods for echinocandins.

We are collecting clinical isolates from all of the patients and doing in vitro susceptibility testing by standard NCCOS methods using different media to try to assess that.

We have seen in the patients a range of MICs at baseline across the aspergillus species isolated. We have not seen a relationship of MIC to outcome in those individuals in the caspofungin study, and in fact, the three individuals who had MICs of 64 or greater all had favorable outcomes. There were probably a number of factors that may be due to that.

We've tried to look in all of our studies, not just the aspergillus study, but also the candida study, to try to collect isolates on patients who fail or relapse and to look at susceptibilities in those patients and whether they change in patients who fail if they go up.

The data from the aspergillus study are limited because of the difficulty in getting follow-up cultures in those patients. In the few patients where the data are available, we haven't seen any increase in MICs.

We've done a similar thing with the patients in our candida trials, looking again for changes in trends of increases and have not seen that,

but we recognize that because this is a new mechanism of action, that we're collecting the isolates, trying to use information as we gain it over time to try to get a better understanding about it.

DR. FLETCHER: And lastly for me, I'm looking for a little, I guess, maybe more information about the design, the design of the 019 study and the historical control study. Were these designed as, if I can use the word, as a package?

In other words, you know, we're going to conduct, you know, a non-randomized study and compare it to an historical control, and it was conceived, you know, if you understand what I mean, conceived of a package or, you know, were these done in a sense separately?

DR. SABLE: The question regarding the timing and design of the two studies is one I think that's worth going through. The caspofungin noncomparative study was designed initially as a stand alone study with the design intended to obtain some data on efficacy and safety in that population.

As we had early promising clinical results and met with the agency to discuss those, among the things that we discussed were expert review of the cases, as well as designing a historical control study

of the type that we thought would try to address the issue of placing the data from the study in context.

So the two studies were not designed at the same time, but with the historical control study, we certainly recognize that there are multiple biases in the study. Some are for caspofungin and some are against, and that it's impossible in any type of design or analysis to completely eliminate those, but that no matter how we've looked at the data, and we have looked at it in a variety of ways, the data are robust. The trends and the conclusions remain really the same.

And it's not our goal or objective to say that caspofungin is better than standard therapy, but rather to say that the data from the historical control study support that caspofungin is effective.

And we've actually looked at several of the things that have been pointed out as far as potential issues for that, including the duration of therapy, and if you take patients who died during the first 14 days of treatment, so extending beyond seven days, you have a slightly higher response rate, but it certainly doesn't change the overall outcomes.

And if I could have the slide, I can just show you what this is.

So if you excluded patients who died early, the response rate is not 17 percent but, in fact, 23 percent. We've also looked at U.S. versus Europe and used region within the logistic regression model, and once you adjust for the other factors, and if you add region in U.S. versus Europe, it doesn't come out as a predictor of outcome.

And we've looked at common sites and year of entry. So we've tried to look through some of the things, and the only thing I can say is even though they weren't designed at the same time and recognizing the limitations, that really the results are consistent across different ways of looking at the data.

ACTING CHAIRMAN GULICK: Dr. Stanley.

DR. STANLEY: Thank you.

Getting back to the resistance question, just when you gave your presentation you alluded to having done in vitro studies to try to elicit resistance or to try to develop that. Can you expound on that just a little bit?

DR. SABLE: I'd like to actually ask Dr. Dennis Schmatz from our Basic Microbiology Group to address that.

DR. SCHMATZ: As Dr. Sable alluded to

earlier doing resistance studies with aspergillus is quite difficult because of the quantitation issues and it being a filamentous fungus. So we focused all of our efforts on sacromices (phonetic) as a model in the lab and Candida albicans as a model for the pathogens we're interested in.

And as Dr. Sable pointed out, there is this frequency when you select without any type of mutation that is in the range of one in ten to the eighth. We've mapped that resistance from the laboratory. It's only in laboratory situations that we see this. We've mapped this resistance, and it always maps back to the same one protein, a protein identified as FKS.

It's an essential gene, and we haven't seen any other cases of resistance that are not related to that specific gene.

DR. STANLEY: And does that gene activity -- is the protein from that gene, the activity, get impaired with mutation?

DR. SCHMATZ: Yes. The FKS gene has 16 transmembrane domains. It's a very large protein, and while it's not proven definitively that these confidence blocked glucan synthase because no one has finally proven that's what this is, it's a member of

a complex of several proteins that are in vitro when you make a membrane preparation from these cells, will produce beta-(1,3)glucan. You can inhibit that with these compounds.

When you get a mutation in FKS, you can see a change in the susceptibility to the glucan synthase inhibitors.

DR. STANLEY: Okay. Thank you.

Another question regarding the pharmacokinetics and metabolism. You state that the distribution into tissues is really the mechanism of handling of this drug, and I just wonder. I didn't see any data in the background materials on looking at longevity of this drug or its metabolites in tissues or at various tissues. I just saw mention in the liver.

DR. SABLE: Can I ask Dr. Stone or I'm sorry. Dr. Pearson, metabolism, to address that.

DR. PEARSON: Your question is regarding longevity of metabolized in tissues, and we do have some data on this, and we conducted tissue distribution studies in rats where we have actually examined levels of drug related material at various time points.

I do have some slides if you'd like to see

those. Dusty, Slide 14, 1418, please.

This slide show the various tissue distribution of caspofungin, and this is actually drug related material shown in terms of radioactive equivalence across a range of different tissues, and this is following half an hour of two milligram per kilogram IV dose, and this represents essentially, even though this is radioactivity, this represents essentially caspofungin.

And we see at earlier times it's very broadly distributed, and in the next slide, please, we recognize that at a 24-hour time point we actually see high concentrations in the liver and also high concentrations in the kidney.

So this really reflects the distribution of the compound where the compound is take up into liver, and this is a fact that actually modulates the pharmacokinetics.

Does that answer your question?

DR. STANLEY: Have you gone past 24 hours?

DR. PEARSON: Yes, we do.

Next slide.

Yes, we have data at 12 days as well, and this shows at 12 days following IV as a single dose that we actually have high concentrations in the

liver, about two microgram equivalents, and also we see some drug remaining in the kidney as well.

DR. STANLEY: I guess I'm interested in that because of the data that you did discuss briefly about the binding to proteins, and you call it an irreversible binding of radioactivity to proteins.

I saw a measurement out to 20. Was it 20 days on that? How long have you looked at that and also the protein binding?

DR. PEARSON: Sure. I can answer that as well.

Your question is regarding binding to proteins and what have we actually measured, and I can actually probably give you quite a bit of additional information regarding binding to proteins and try to explain what's actually going on and what this actually means.

And my first slide I'd like is 1443. Fourteen, forty-two, please, Dusty.

This slide talks about the binding of radioactive caspofungin into proteins, and we observed covalent binding to plasma proteins, which was detected by initial observation of a long half-life of drug related material in plasma of both humans and monkeys.

And what we noted is that following administration of the compound, that the half-life of radioactivitv in plasma was prolonged relative to that of parent drug in humans, monkeys, and rats, and this half-life is attributed to low levels of covalent binding of caspofungin to plasma proteins, and this observation occurred both in humans and also in rhesus monkeys.

And in humans, thought their combining with plasma was low, less than seven picamoles or 1.3 percent of the administered single dose and declined with time, and at comparable time points the level of binding in monkeys was about thee times, five times higher than that with humans.

And these two plots illustrate plasma profiles following administration of [3H]caspofungin to both humans and also to monkeys, and these plots illustrate in the yellow circle caspofungin which declines rapidly following an IV administration, and we see over a 28-day period that in humans there's a terminal phase of radioactivity which approximates about 12 days.

In monkeys we actually also see a very, very similar phenomenon with caspofungin. It declines very rapidly itself, and we actually observe that

there is drug related materials that's high level sin plasma over time.

And when we actually went ahead and characterized this further, we actually took samples from both humans and animals and actually looked at various time points during the terminal half-life, and we actually measured levels of material bound to protein.

Next slide.

And this table illustrates covalent binding of radioactivity to plasma proteins, and we can clearly illustrate at various time points. In a monkey up to day 20 we can actually see covalent binding of drug related material with the plasma proteins, and we can also see the same phenomenon in humans.

An important point here is that we see high levels in the monkey, which are much higher than what we observed in humans.

And we also know a lot about mechanism of binding. We know that this involves spontaneous degradation of caspofungin, which is one of the factors that control the elimination of caspofungin, and this involves the formation of a major metabolite, L-747969, and in the formation of this metabolite,

there are a number of intermediates that are involved, and one of these is an aldehyde, and it may occur in modified plasma proteins.

And its metabolite 969 is a major circling metabolite in humans, rats, and monkeys, and due to the spontaneous nature of the formation of this metabolite, the proposed mechanism suggests that should happen in all animal species and humans.

Does that answer the question in terms of the long --

DR. STANLEY: Yes, just a couple more real quick.

Now, those data were after a single bolus of drug. Have you looked at cumulative data?

DR. PEARSON: No, we haven't. We've only studied single dose and binding of single doses and the long half-life of a single dose.

DR. STANLEY: Okay. And then has any patient, whether they were candida or aspergillus, gotten two separate courses of caspofungin?

DR. SABLE: Yes. Actually in the clinical trials retreatment was not allowed except in two specific studies. It was in our pharmacokinetic study in patients with Candida esophagitis, and in the compassionate use study.

There have been six individuals who have received repeated courses of caspofungin therapy, including a few who have received more than two courses. We've actually looked at those individuals for the presence of any untoward adverse events and have not seen anything that's been different or unusual in those individuals versus those who have received a single course.

DR. STANLEY: Okay. Thank you.

I guess my concern obviously when you're treating aspergillus, invasive aspergillosis, you're dealing with immunocompromised individuals, but as indications if they are ever expanded for this drug, you would be concerned about adverse reactions from being exposed to altered normal human proteins over time, I would think.

So I would just make that statement as a concern if different populations of patients were looked at.

ACTING CHAIRMAN GULICK: Dr. Blackwelder.

DR. BLACKWELDER: I'd like to address two issues that are related. First is I'm having a hard time being really confident about a conclusion about the efficacy because of all the biases we've talked about one way or the other.

I noticed you have in your book that most of the patients in the 019 study who were refractory actually had documented progression of the invasive aspergillus infection. Do you have, or remind me if you've already shown it, please, the proportion of those patients, that subgroup who had favorable responses?

DR. SABLE: Yes. If we look across the patients who had progression on standard therapy, approximately 30 percent of those patients had a favorable response to caspofungin.

DR. BLACKWELDER: And is it -- somebody help me -- is it clear that if that continued on their initial therapy that you would not expect anywhere close to 30 percent to eventually respond?

DR. SABLE: I mean, I think that based on the course of their disease with clear progression, that it would be unlikely that they would, and I'm not sure if anyone else would like to make a comment.

Dr. Walsh?

Perhaps Dr. Walsh who is actually the head of our expert panel would like to make a comment.

DR. WALSH: I'll address just the broader issue, and if there are specific aspects of it that haven't addressed your question, then please feel free

to ask me.

Our panel was convened to examine the data set that was provided through us through extensive extraction and recapitulation from the medical record. The individual materials that we had were comparable to that of the medical record.

Having chaired or participated in these panels before, I think this was really the largest and most robust set of data that we've ever had on individual patients, as well as the detail being provided on individual scans as well as background, concomitant medications, immunosuppressions, resolution of neutropenia, withdrawal of corticosteroids, and the progression of graft versus host disease.

And so in that regard, I think as we reviewed these cases, we truly had a sense of the tempo of infection and the course of infection that generally one doesn't acquire from such analysis without going through the individual charts.

And in that regard, we found that in most situations we concurred with the investigator, but in some instances clearly the investigator had misunderstood or the success criteria, and we clearly censored that.

And when we did disagree amongst the panelists, with further discussion usually it was very clear insofar as where there was misunderstanding, and then sometimes there were subtleties that ultimately any reasonable people would disagree upon, and we just came to resolution.

And using that process, we ultimately came to agree on all but one case, and that was just a gentleman's agreement to say we agree to disagree, but that, I think, reflects in a sense the dynamics of the process, and I think, again, it was extremely robust and very, very rigorous.

And if we had any information that was required that we solicited, the response was extremely prompt. The individual, Carole and her team, would go back to the primary medical record, acquire the information. The data queries were very thorough, and we would have quite literally every bit of information that we needed.

So I think our analysis is really quite reflective of how we were interpreting ultimately the key information that we required, including fine subtleties to assess a clinical response.

Our other impression was that these patients were critically ill. There is no doubt that

these were very immunocompromised patients, comparable to that which one would see in any other setting. Granted from any distribution, depending upon enrollment, one may see more neutropenic patients, more ALBMT, more solid organ transplants.

But if you take those individual categories of leukemics, solid organ transplant, allogeneic BMT, graft versus host disease, they were easily comparable to that which any of us with experience in those patient populations would have expected to see.

DR. BLACKWELDER: I still have one question. We've just heard that about 30 percent of those whose aspergillus infection was actually getting worse responded once they were put on caspofungin. Are you confident that you would not have seen any favorable response rate close to that had they continued on the therapy they were already on?

DR. WALSH: We took actually two levels of review. Within our own unit, that is, the Immunocompromised Host Section at the MCI, we reviewed all of these cases separately, and then we then convened with the chair, and then I had not only my own perspective just to ascertain that I was correct in my own assessment, but also that of the input from

my whole section.

And so in that regard, we looked for that particular issue, and we asked the question: well, were these patients really failing?

And in many instances they were. There were sometimes a few cases were there was recovery from neutropenia, and I would submit perhaps in the setting of neutropenia, if the patient was profoundly neutropenic and remained neutropenic, it was almost invariable that those patients were not going to survive or do well, and I think that's just a reflection of virtually any antifungal agent that we have, and that is an ominously poor prognosis.

But when patients did recover from neutropenia, they responded, but that was only a small fraction. As you know, they're only approximately 20 percent of patients that were neutropenic.

The other patients who were not neutropenic and often remained under corticosteroids or other immunosuppressives, because of transplantation or graft versus host disease issues, had much less in the way of modulation of their immunosuppression, and these were patients who clearly were progressing, were started, and in many instances did respond.

So in that regard, particularly in the non-neutropenic patient population, we were not struck that alteration of immune modulation played a role and that clearly these patients when they came in with progression really were progressing, and as a group we also addressed this in our panel discussion, and we were quite certain that they fulfilled that criteria.

Indeed, there is a check box insofar as whether these patients were progressing, and we addressed that specifically. Were these patients progressing? And we addressed it both in my section as well as in our panel, and we had the option of say, no, these patients did not fulfill progression, and we agreed that in virtually all cases that it was appropriate and that they were progressing.

So I think we seeing some benefit. In a way, at a more preclinical or basic level, it does make sense. There organisms obviously have ways of circumventing through subtle means of emergence of resistance perhaps, and this is the subject of investigation of several laboratories with polyenes, for example, up regulation of catalase, dampening of the lipoparoxidation (phonetic) that takes place, and some of us believe that that may be a means by which these organisms circumvent the presence of a polyene

even though you may have peak plasma concentrations.

There's also the issue of tissue penetration of a very lipophilic drug, such as amphotericin, that may not penetrate into the area. Hence, if you come in with a different agent, you may actually be hitting that organism when a polyene may not be getting access to it.

There's also the other effect that you may have carryover of polyene as well in the tissues that just may not be adequate to eradicate that organism. You come in with a second agent, an echinocandin, a cell wall active agent, and the potential synergy between the two may actually be significantly greater than either agent in itself.

And we have experimental data, several laboratories with experimental data, to support that. So I think there is both a preclinical and a clinical rationale to say, yes, some of these patients were progressing, and, yes, indeed, they did respond to compound legitimately.

DR. BLACKWELDER: Thank you.

The other issues about the design of the study, of 19.

DR. WALSH: You mean the 019.

DR. BLACKWELDER: Yeah. What's the real

barrier? I guess this is really relevant to any future studies, too, but what's the real barrier to have done a control randomized study? Do people believe the patients just don't exist? There aren't that many or is there some other real reason you couldn't do a randomized controlled study?

DR. CHODAKEWITZ: Maybe I'll just answer briefly and also ask Dr. Sable to comment.

I think partially one of the biggest barriers is the kind of patients, and I think that was really implicit in Dr. Welsh's comments, that these are patients who are very sick, who have people in that category, as he said, who are progressing, have a very high mortality. I think that, you know, his comments reflected that we think very few of those patients would have responded.

And then you're confronted, given that clinical reality, with how do you deal with randomization to what do you randomize those patients to?

And Dr. Sable can comment, but I think it really is intrinsic in the very poor prognosis in this kind of patient group and then need to deal with issues of individualization of their therapy.

DR. SABLE: I don't actually have anything

else to add to that.

ACTING CHAIRMAN GULICK: Would Dr. Stevens or Graybill like to address that issue?

DR. STEVENS: I can speak to this point, probably have the unique history of probably being the only person in this room who has presided over a randomized trial that failed.

(Laugher.)

DR. STEVENS: So I can tell you that that's a very, very difficult thing to ask for, although it's still the gold standard and must always remain the gold standard, Bill, as you pointed out for reasons that have been mentioned by Jeff, but for other reasons.

There are competing protocols out there. The patients are scattered between a number of institutions, and our feeling was trying to do that study and a study subsequently, that it probably would take a cooperative effort on the part of both the Mycoses Study Group and the EORTC together to do a randomized study of that type. It really would require that magnitude of numbers of patients to get there. So it's really tough.

I think that's what it comes down to. As somebody who went down with the ship, I can tell you

I think it's a really tough thing to ask for.

ACTING CHAIRMAN GULICK: Dr. Goldberger.

DR. GOLDBERGER: Yeah, I just wanted to see whether any of our invited guests wanted to comment, if anything in addition to Dr. Walsh's comments in response to Dr. Blackwelder's question about the 30 percent response rate in terms of patients who were progressing.

If any of you wanted to make any observations about, you know, what you might expect if patients had been left on their previous therapy.

DR. GRAYBILL: I can add a little bit to that. These people are desperately sick, and if you're functioning as the physician rather than investigator and death is an imminent endpoint, one wants to do something, anything.

Given some of the patients that have been reported with ALOBMT patients with mortalities in other studies reported as high as 90 percent, you could probably justify giving, you know, IV porcelain because that will probably be as good as amphotericin or anything else.

We've done terribly with this disease, and 30 percent, I think, you know, is fairly optimistic with some of these people.

As several people have made, Dr. Perfect earlier, the new therapies that have been implied, voriconazole, for example, presented at the IDSA meeting about a 40 or 50 percent, 51 percent, I think, response, right in a similar study, salvage study.

Posaconazole, I think the data were shown earlier here with response rates at about the same rates. The problem is that the populations are small, and the patients are desperately ill, and to find these hard documented patients is really tough, and we're looking at licensing a drug for salvage therapy of well documented disease that is uncommon.

So why should one be interesting in licensing a drug for aspergillosis? It's because of what people have alluded to before. If you can get there ahead of the curve, you might do much, much better. One of the things I am most interested in is where we stand with the antigen based diagnosis.

You, Dr. Turner, may know more about this than I do with the evaluation. I just very much hope that that's going to work and be licensed, and if that is, and if that gives us access to patients earlier, we might be able to get to a patient before they become so desperately ill.

The EORTC is already inserted or accepted

serologic, diagnostic criteria from the U.S. There is a panel that met and agreed to change the U.S. definition for aspergillosis to include specific lesions on CT scans and serodiagnosis, all in an effort to get a diagnosis earlier so that we might get there before we're just at the very end of the line, when half of your lung is infarcted and the patient has a brain abscess, and there's just almost nothing to do.

So what do you use these things? I think the populations will change, that we will be treating earlier aspergillus as, God willing, we get these new assays on board to let us get there earlier, and we will probably be treating a larger number of patients who, one, are better than just fever and neutropenia because they have some evidence for aspergillus, but, two, are not all the way bowled over with disease and about to die.

And I am really hopeful that any of these agents may be used at a much earlier stage. And all of the arguing about 30 percent or ten percent of these terrible mortalities that we've seen in here and terrible response rates may be better because we're going to treat a whole new and hopefully larger population of patients and do better.

That may not be a straightforward response to your question, but it sure is where I want to go, and thinking of that, I just wonder what Merck is going to do as soon as this drug gets licensed, whenever it gets licensed. There are going to be doctors who say, "Huh, these doesn't knock you over and kill you. I'm going to give a lot of it. I'm going to give it to my people who I'm sure have aspergillus. I'm going to give it to people who I'm afraid have aspergillus. I'm going to give high doses of it perhaps." I don't know how much, and the question was raised. It'll probably be used in cyclosporin patients pretty soon.

That raises a little bit of a concern for me because if Merck doesn't get there real soon with data on cyclosporin, we may have very unclean information coming out from the practitioners out in the country. WE may not know what to do with it if there is a real interaction or if there isn't.

So I think Merck has given us very good data on a small number of patients, but I am concerned that we have more data and, you know, an aggressive look at some of these concerns of doses and timing and earlier initiation of therapy or febrile neutropenics.

So there are so many other things that

bear on a large population that is likely to receive this drug.

Sorry for being so long.

ACTING CHAIRMAN GULICK: Do others wish to comment on the specific question about the 30 percent response rate?

DR. PERFECT: That's an impossible question to answer. These are too complex of patients to know if you continue to treat them whether they get better or not. No one has that data. They don't know.

What they're trying to influence to you is to say that they probably made some impact on the clinical outcome by giving this drug. But could they have kept on the same drugs and done the same thing? Who knows? These are really noisy, noisy patients.

The thing I just wanted to quickly make -- and no one makes anything quick around here -- but I want to reemphasize one particular point as a clinician, that the question on cyclosporin is a small question, and Dr. Fletcher brought it up and now Dr. Graybill brought it up, but on the wards, taking care of these patients, I don't want any more liver toxicity than we have to. These are severely ill patients. They have a lot of toxicity issues.

However, remember this is a salvage drug. This is a drug of last resort, frequently used in patients with cyclosporin, and these are not healthy patients, and they are getting constant monitoring.

I think you need to look very closely, and when you give a recommendation, a black box thing, of not recommending cyclosporin and caspofungin together puts the clinician in a tough situation. They're going to have to make the decisions on this thing.

And, in fact, I think it may inhibit the use of this drug significantly, and I would like both the group, Merck and the FDA, to look at this particular question of not recommending its use in cyclosporin if this drug becomes approved because I think it will become a clinical battleground out there or at least some type of criteria to set up to follow these patients very closely because that's real life out there, and that's where this drug is going to be used with that particular compound.

DR. CHODAKEWITZ: Could I potentially just comment, Dr. Gulick?

ACTING CHAIRMAN GULICK: Sure.

DR. CHODAKEWITZ: Just because I think a couple of questions were raised, I think, very legitimate and important questions, and I think I'd

like to just respond back to them.

I think that we agree, first of all, in terms of Dr. Perfect's comments regarding cyclosporin. We have moved forward. We're trying to obtain more data. We'd like to have it done faster. We're trying to do it as rapidly as we can, and we are firmly committed to doing all of the necessary studies in terms of the current studies and any other studies that are needed to gain the appropriate experience with cyclosporin because we do believe that that's an important clinical issue.

I think also, just to be real clear in terms of your comment about dose, we also agree there that we're really ready and are committed to doing additional studies, Phase I studies, to go with the doses above 70 milligrams, and then trying to assess those doses in patients to really learn more.

We recognize that there will be some limitations in what conclusions perhaps may be drawn because of the complexity of the patient as has been stated, but we really are committed to doing that and are going to proceed along those lines.

So in terms of just being able to express the commitment to address both of those important issues, I can assure you that we're committed to doing

that.

ACTING CHAIRMAN GULICK: We have time for some more questions, and then we'll move in to beginning to consider the questions posed to the committee.

So informational questions. Jonathan Schapiro.

DR. SCHAPIRO: Regarding the resistance and possible also drug exposure, since 50 some odd percent of the patients who receive the therapy did die, was tissue obtained from those patients post mortem, possibly the tissue of the infection itself, which could give us information regarding resistance, regarding drug exposure, and maybe help us understand why despite the therapy this large number, try to delineate what were the cause of the underlying infection, I think going back to Dr. Perfect's opening remarks.

The question is: can we do much better than this? And that might help us work that out. Is that tissue available?

DR. SABLE: To kind of divide your question into tissue concentrations and drug and development of resistance because I think they're related but might be slightly different, if we look at

tissues from patients, we have not to this point in people assayed levels of caspofungin in people. We have measured plasma as you've seen with our plasma pharmacokinetics.

We have obtained data from autopsy wherever possible, looking both at the pathology, as well as microbiology data, and have attempted to get those isolates whenever they're available.

The number of patients for whom we have isolates available at the end of therapy is small. Recognizing that there's not standardized testing methods, we've tried to look at the MICs in the beginning of therapy and the end of therapy and have not seen increases, but recognizing that this is an important issue, we will continue as we gather more information to try to better understand that.

ACTING CHAIRMAN GULICK: Okay. Dr. Wong, and then Dr. Mathews.

DR. WONG: I want to get back to the issue of, you know, what would have been expected to have happened if the patients had continues to receive conventional therapy or received a different conventional therapy, and I really have two questions.

One is just to return to the other question. Did you really think it would have been

impossible to design a trial in which at the time a patient was determined to have been refractory or intolerant that he could have been randomized to receive caspofungin or a different conventional therapy at that point? That's question one.

And then question two is sine you didn't do that, and since, you know, we now have a data set in which we have to try to compare the observed outcomes with the outcomes in historical controls that you know, we all acknowledge have problems, I mean, did you going in have a target efficacy rate that you thought, you know, would have been what you wanted to see and below which you would have decided this was an inefficacious drug?

DR. SABLE: To kind of take your question in two parts, as far as the issue of doing a randomized comparative trial, I think that we thought about that, talked about it, and for the reasons that have been mentioned, felt that it would not be possible to do.

And so that's why we went on as has been done with other types of drugs in this type of indication and done a noncomparative study and really tried to put in place strict criteria so that we could convince ourselves, as well as others, that the

patients really had disease, and that patients had favorable outcomes that they really did.

And the historical control is really just designed to provide some additional context to that, and I think that's the reason why a lot of things about progression of disease, you know, patients for whom you don't have a lot of options, what their outcome is.

When we started this study, we thought and tried to make an estimate of efficacy, but realizing at that point that because of the number of factors that we've discussed here today, including underlying disease, site of infection, that it would be impossible to predict because the differences are so great across those populations to be able to pick one outcome which would say if we have this it would be effective or not.

We did define in our comparison to the historical control, looking at the logistic regression model, and said that if our lower bound of the confidence interval was .7 or greater, then we would conclude that we were as effective as standard therapy, recognizing the difference between salvage or primary.

So that was what we had done in trying to

put the study together.

DR. WONG: And how would that have translated into a combined, complete, impartial response rate? You know, .7 confidence interval compared to the historical controls, I mean, that would have gotten you down to what, ten percent or thereabouts, right?

So anything greater than ten percent is a positive result?

DR. SABLE: I'm sorry. I'm not sure of that.

DR. WONG: What would you have considered to be a negative result in this study? You know, what response rate would have led you to conclude that the drug did not work?

DR. CHODAKEWITZ: Let me try. I think there are two ways of sort of addressing your question. One is a more statistical way. Let me try first, and then we'd certainly be happy to address that.

I think that we did it in two ways. I think, first of all, we used the confidence interval as Dr. Sable mentioned, and I think it's important to point out because I understand your concern about this, is that we didn't know what the outcome of our

historical control study was going to be when we made that definition in the confidence interval.

So a priori we didn't have a number, but we knew that we were going to, without knowing what the result from the historical control study was going to be, we said this is the range on a relative scale that it would have to be for us to conclude at least similarity.

So I think in a general way, we made our definition independent of the actual numerical values. I don't know if that's a sufficient answer. I can also ask others to comment in terms of the statistics, but I thought that was trying to get at the spirit of your question.

DR. REX: John Rex, University of Texas, Houston.

I want to come back to Brian Wong's question about the feasibility of having done a randomized study. Dr. Sable gave her answer that it had been debated. Let me just expand upon that and say that it was debated extensively in the room, Dr. Walsh, Dr. Patterson, others, particularly at the Mycoses Study Group and other forums.

We desperately wanted to see a randomized study and could not come up with a good way to get at

this, and the comparator was really the sticking point. There wasn't anything licensed that would be acceptable. The only licensed drug really is amphotericin, and remember this was several years ago, kind of before the lipid amphotericins had come into their own.

It might be possible to see that now, but even so it's very, very difficult due to the different things people have come into. It's very hard to randomize somebody to an arm that might be lipid ampho. when they've been failing lipid ampho. What do you do?

So I just wanted to reiterate that a lot of thought went into trying to come up with a way to do a randomized study, and David Stevens' example of a randomized study that didn't fly because it was just so hard has sort of colored that.

DR. WONG: Right. I mean, I understand that, but, you know, the results of that decision are that we now have to try to interpret data that are very difficult to interpret, if they're interpretable at all. And you k now, that's where we are.

ACTING CHAIRMAN GULICK: Dr. Mathews.

DR. MATHEWS: I have a couple more questions related to the comparability of the

historical group to the active drug group. One issue relates to the time course of neutropenia and steroid use.

If I recall correctly, you presented data on baseline status and then also I think some data on people who were neutropenic throughout the course and their outcomes, but did you do something like Kaplan-Meier analyses at time to resolution of neutropenia, time to reduction of steroid dose to less than 20 milligrams, comparing the historical group to the --

DR. SABLE: No, we had not done that specific analysis. As you mentioned, we looked at characteristics at baseline, and then what happened to patients through the course of the study and at the end of therapy.

In the historical control study with the retrospective chart review, it was more difficult to get precise information. So the time course information that you mentioned we did not look at.

DR. MATHEWS: Okay. Well, obviously I think that's important kind of information if it could have been gotten because, as anybody knows who's treated these kinds of patients, the resolution of those abnormalities can clearly affect outcome.

Did you want to comment?

DR. CHODAKEWITZ: I just wanted to add I think that we also had the limitation of small numbers of patients in any given cell, and so what we tried to do was use the still on or not still on high dose steroids or something like that.

The analysis that Dr. Sable provided is not as rich as a Kaplan-Meier curve, but it was really aimed at trying to address the same question that you're asking about.

DR. MATHEWS: Okay, and I think my next questions relate to some data that were presented by Dr. Navarro, but it deals with adjustment for potential confounders and the comparisons that were made, and the sponsor's presentation, I think, Slide 97 where you showed the crude and adjusted odds ratios in the logistic models and showed fairly consistent effects that would suggest superiority of caspofungin.

And in Dr. Navarro's presentation, however, Slide 41 in that presentation which gave the duration specific response rates, and it went by very quickly, but I think to my mind it was very important because it clearly showed a major potential confounding in the comparisons by duration of therapies, and if you look at the stratum specific odds ratios by duration, they go from .95 to 1.47. I

don't know what it would be if you pulled all of that, but clearly it would be equivalent, no superiority compared to the unadjusted odds ratio, two and a half or so.

And while I realize that the indication you're going for is clearly not superiority, I think the implication from the analysis you've presented, the confidence interval, even the adjusted analyses do suggest superiority.

I think this analysis calls that seriously into question.

And the second point is the temporal trends that were in Dr. Navarro's presentation. I forget which slide it was, but where the improvement in outcomes for 1995 to 1998 went from something like 12 to 20 percent, and you know, making these comparisons really assumes that the historical group you'd like to be able to say was comparable in every way to the treatment group, except for the fact they didn't get the drug.

And if you've got those kinds of temporal trends and extrapolate it to the same time period of the 019 study, you end up with a response rate of around 27 percent, if my seat-of-the-pants calculations are accurate.

So I come away with this with the clear impression that these two interventions are probably equivalent, but there's certainly no evidence that caspofungin would have been superior had it been a back-to-back comparison at the same time.

DR. SABLE: There's actually several points to your question that I'll try to address logically, and please let me know if I miss something.

The first regarding superiority versus equivalence, I think that there's a difference between what the statistical tests show in the formal comparison using logistic regression that we did and the conclusions that we think we can draw from the study, and that's because of the nature of the studies.

It's a historical comparison. It wasn't a prospective, randomized comparative trial. So we aren't trying to conclude that caspofungin is superior to standard therapy, but to say that the comparisons in all of the ways that they've been performed provide support that caspofungin is effective.

If we take the two parts of your question regarding duration of therapy and then year of treatment and outcome separately because I think that they are two separate issues, if we look first at

outcome over time, and the numbers that Dr. Navarro did present with the differences in response rates, if I could please have the slide that shows the outcome over time.

If you look numerically at the outcomes between -- numerically at the response rate in each of the years, the numbers of patients abstracted in each year are small, and in fact, the confidence intervals, as you can see, that there's significant overlap.

When we've actually put in the logistic regression model after adjusting for the other factors, year did not come up as being another important predictor of outcome. Recognizing that, there may have been some other differences between the patients in 1995 and '96 and the patients in '97 and '98.

We've actually also done a comparison looking at the patients only included in the later two years. So 1997 and '98, which would be compared to the patients in the caspofungin study that were enrolled in 1998 and '99, and the conclusions of that comparison are the same, if you could just please.

As you can see, the response rate in the 133 patients in the historical control that were abstracted in the latter two years had an overall

response rate of approximately 20 percent.

We realize that because they're not done at completely the same time, it is one of the limitations of the historical control study, but it is one of the reasons that we tried to get some of the sites. In fact, we enrolled the majority of patients in both studies.

Okay. To turn now to the duration of therapy, I think that there is a difference in duration depending on when you count the start of therapy, and there's a difference between total antifungal therapy and antifungal therapy as part of the study treatment.

If you look at total duration of therapy, including the prior treatment that patients received in caspofungin, that duration plus caspofungin is in excess of what was seen with the standard therapy and the historical control.

However, over 80 percent of those patients were refractory to that therapy, many of who as we've discussed actually had progression on that disease. Their outcome after that was clearly a change in course.

In contrast, intolerant patients received much shorter courses of treatment. So we would

consider looking at duration of therapy from the initiation of caspofungin therapy and the initiation of standard therapy.

If you look at the durations in those two groups, they're actually very similar.

Does that address your concern?

DR. MATHEWS: Well, I guess I would like to see, and I don't expect you to have it necessarily, a similar table then showing the response rates by those strata of treatment duration.

DR. SABLE: One of the things that we have done, as we had mentioned earlier, patients who had to receive a minimum of seven days of therapeutic doses of the antifungals, we've gone back and looked again and said, "Okay. We're going to only include patients who have received at least 14 days of therapy in the historical control," making it closer to the duration in our study, and the response rate instead of 17 percent is approximately 23 percent.

And you can go on and do further cuts, but eventually you do get to a point where you're talking about the natural history of aspergillus, and it's just one of those differences, but even excluding patients who have received less than 14 days of therapy, the conclusions are still the same.

DR. MATHEWS: Thank you.

ACTING CHAIRMAN GULICK: Dr. Kumar.

DR. KUMAR: Dr. Sable, may I ask you two questions related to safety, to your adverse events? The first one, and that was shown in Dr. Navarro's presentation, it was the full last slide in which she showed in her table that candidiasis was more common in the group of patients who got candidiasis. Would you comment on that? Why should that happen?

DR. SABLE: I think it's one of the difficulties with looking at data from a complicated database. Many of the patients that were included in the 330-some patients were patients who were enrolled in the candida studies, who had either Candida esophagitis or pharyngeal candidiasis at baseline.

The way that the information can be reported is investigators may choose to report the occurrence during treatment or afterward as either an adverse experience because of progression of the disease or as a relapse.

The information that's collected in safety only includes the patients who have actually had reported as adverse experiences.

We've looked across the studies and across the doses, and relapses occur. Most of them occur

when patients are off treatment, as you would expect, since most of the patients in the candida studies had advanced HIV infection with CD-4 counts less than 50.

DR. KUMAR: Thank you.

My second question relates to fever as an adverse event. Could you tell us a little bit more about that fever? When did that fever occur and how long did it last?

DR. SABLE: Fever was actually common across all of the treatment groups in the candida studies, and the information as far as the specific temperatures were not always reported because they're reported as fever as an adverse experience.

We collected temperatures related to infusion and have that data, but as far as being able to tell exactly how long the fevers lasted, I can't tell you that.

What I can tell you is that they didn't lead to discontinuation of therapy, weren't considered serious adverse experiences, and in these very complicated patients were often due to underlying diseases, concurrent conditions.

Does that answer your question.

DR. KUMAR: And then if I could go back to my final question, I asked you this earlier on in the

morning.

DR. SABLE: Yes.

DR. KUMAR: Would you be able to show that your efficacy rate in allogeneic bone marrow transplants?

DR. SABLE: Yes. I can actually tell you. I can't show it to you.

The patients who had hematologic malignancies without transplants, 11 of 21 had a favorable response, or 52 percent. If we look at specifically patients who had allogeneic bone marrow transplants, six of 16, or 37 percent, had a favorable response.

We went back and looked at the data for graft versus host disease, and this is graft versus host disease at baseline. One of the ten patients reports, who had graft versus host disease, had a response in contrast to two out of five who did not. There are, of course, as you can tell, a number of patients for whom the data weren't reported.

We also looked at patients who developed graft versus host disease on therapy, and one of the six patients who developed worsening graft versus host disease had a favorable response.

DR. KUMAR: Thank you.

ACTING CHAIRMAN GULICK: Dr. Hajjeh.

DR. HAJJEH: Yes. I'd just probably I'd say follow up on many of the other questions that were asked, but you know, I think a lot of these questions could be answered by further analysis of the 019 and the comparative or the historical control trial.

Regardless of all the limitations you have, which can also be controlled for somewhat, I mean, you have for every case in your caspofungin trial, you have almost three historical controls, and for example, to account for the 30 percent response rate in the patients who had progressive disease when they were entered in the study, I mean, I was wondering whether you tried to compare them to a group or a subgroup of historical controls who actually were at a similar stage when you looked at them and what you can get out of that.

DR. SABLE: As you mentioned, we do have a lot of data on both of these studies, but one of the differences is, of course, as we've discussed, the fact that caspofungin is a salvage study, and the patients in the historical control are primary therapy.

So the assessment we made was at week one, which would have been the minimum criteria for entry

into the historical control. Although we didn't find match controls, we used the logistic regression of attempting to adjust from multiple prognostic factors within individual patients as a mathematical way of trying to do that as opposed to finding controls.

DR. KUMAR: True, but within the historical controls, you cannot identify a group where, you know, not necessarily at seven days like the caspofungin trial, but maybe later where the physicians decided that these patients are not doing well and they decided to switch them to alternative regimens, and how did they respond after that?

DR. SABLE: I think as Dr. Navarro mentioned this morning, that was one of the things that the FDA had actually done. It identified a cohort of 96 patients, and they had a response rate of 19 and 20 percent.

And I'm not sure if Dr. Navarro had anything else she wanted to add to that.

DR. NAVARRO: We could not attempt to do much more analysis because the information was limited, but we did try to come up with a population that was analogous to 019, and the numbers do speak for themselves.

We did see a 19 to 20 percent efficacy

rate in that population.

DR. HAJJEH: Yeah, but you know, the one thing also that was not controlled for is the type of therapy that was provided prior to that and whether you could label it as adequate therapy or what are the regimens and what would their effect be on these patients after being in the trials or the historical controls?

DR. SABLE: We actually counted therapy as therapeutic doses of antifugals. So the duration of treatment in the historical control is only therapeutic doses. It's not prophylaxis.

DR. HAJJEH: Yeah.

DR. SABLE: So as you mentioned, there are limitations to doing historical control studies, and we certainly recognize that. We've tried to explain some of the things we've tried to put in place.

DR. HAJJEH: But that's my point, that further analysis is really warranted. I mean, the amphotericin, you cannot really just rely on the number of dosage. You have to rely on the total amount that was provided and the number of dosage by itself might not be your best parameter to use to control for clinical efficacy.

But, you know, the other thing also in

regards to Dr. Mathews' question, I think the numbers that are presented in that Slide 41, I think, that Dr. Navarro presented, what we have here presented to us is really the raw numbers without being adjusted for the duration of therapy in the various subgroups.

And if you look at this table again, Slide 41, would you please show that?

DR. GOLDBERGER: We unfortunately have the less expensive Proxima.

(Laughter.)

DR. NAVARRO: We just bought a more expensive one, and I'm going to assist with a new one.

DR. HAJJEH: Well, we have similar problems at CDC. It's government problems, but okay. I have the slides.

The point I want to make is that in the 019 study 18 out of 63 patients were on over 100 days of therapy, which is almost like 25 percent of all patients. However, in the historical control group, only nine out of 206, which is less than five percent, were on over 100 days of therapy.

You know, you might choose a different break point, 25 days or more, but the idea is that instead of coming up with a 17 percent clinical response in the historical study, I think we should

just have an adjusted clinical response rate, and it will be adjusted for the duration of therapy. I mean, it's a simple statistical thing to do.

DR. SABLE: I mean, I think that one of the difficulties certainly is that if patients are doing well, they're going to be receiving treatment longer, and after they're entered into the study, that becomes more of a reflection possibly of outcome.

I'd like to ask Dr. Gary Koch.

DR. KOCH: Yes, I'm Gary Koch. I'm with the University of North Carolina as a statistical consultant.

The question you raise is very interesting. It also arises in randomized studies because in a randomized study if one treatment has significantly better survival than the other treatment, it's going to have longer duration of therapy because it has better survival.

Now, you have to separate duration of therapy in terms of what came after study entry and what came before study entry. Now, what came after study entry is part of the treatment effect, and if longer for the group where the outcome is more favorable.

Now, what came before study entry is

something one could conceivably control for. Now, my understanding is that for the historical control group, it's basically seven days because the decision was made to enter someone into 28 or 29 at the time point of seven days if they fulfilled the relevant criteria.

For Protocol 19, it was seven days to some greater length of time while the patient was being treated until they had met criteria for being refractoried.

Now, what those amounts of time prior to entry translate into is not clear. I mean, certainly we could look at that as another candidate for adjustment, although we've already adjusted for a number of prognostic factors that reflect relative benefit in the control group, but in the control group they're all entering at seven days, and the way in which the prognostic factors were identified was to identify the factors that were predictive in the control group.

DR. HAJJEH: Sure, and I understand that, but in the control group they're all treated anyway with whatever the standard therapy is. So all that I'm saying is that when you present the final clinical response, which is 17 percent, this is just the

overall response rate, but it's not adjusted for the different proportions of your patients in the different strata of therapy, and this could be done.

DR. KOCH: Yeah. You know, a stratified analysis because the sample sizes are small is really achieved with a logistic regression, and the time to event was shown for you in terms of the mortality outcome in terms of the Kaplan-Meier curves.

But the notion of one group had people treated longer is mainly a consequence that they're surviving longer and they're responding, and that's why they're essentially getting longer treatment.

DR. BLACKWELDER: I don't quite see that because in the 019 -- I mean, I agree with Dr. Hajjeh. I don't see why that's not a relevant analysis by the one that's stratified by direction of therapy because in the 019, the patient had to have survived a lot longer than seven days in order to even get in the study if they were not considered refractory until then; isn't that correct?

DR. SABLE: If I could just comment, patients were required to receive a minimum of seven days of therapy in the caspofungin study before being declared refractory, but they may have received longer course of treatment, and again, the difference between

that as salvage and the primary therapy in the historical control.

As I had mentioned earlier, one of the things we have done is looked at patients in the historical control study who died during the first 14 days as kind of the next step, and the outcomes in those patients was 23 percent as opposed to 17 percent.

And what eventually does happen is if we keep going out farther, we could eventually get to 100 percent in the historical control, but what we're trying to do is to at least say that even if you extend longer in this primary therapy study population, that you still see a benefit with caspofungin, and I think it is one of the challenges of trying to do this type of study where patients are required to fail something else first in comparing it to a primary therapy population.

DR. BLACKWELDER: Exactly, and the analysis to make them more comparable with respect to this particular variable seems to be the one that Dr. Navarro showed where in both groups they had to survive a certain length of time in order to get into the longer duration of therapy, but it seems to me that's true of both studies.

DR. KOCH: Yes. I mean, what you have is that in Study 019 the number of days before study entry could vary from seven days to something longer than that, whereas in Study 28 or 29, it was seven days.

Conversely, the patients entered Study 19 on salvage therapy, having failed whatever they had been on at least in someone's judgment. Whereas they entered 28 or 29 on the basis of not having improved, and the way we attempted to try to balance these things was simply to try to identify what other factors other than this number of days prior to entry to the study were correlated with outcome, and we controlled for that.

But when you talk about long durations of treatment, most of that comes after they've entered a study, and as I said before, if you're in a randomized study comparing A with B, if the people on A survive longer than those on B, they'll be treated longer if they're getting treatment every day.

So the time that comes after study entry is not a source of bias. That's part of the treatment effect. The time that preceded study entry does have ways of differing for the two groups, but also the one group entered as salvage patients, and the other group

entered not exactly as salvage patients, but we tried to adjust for all the things that we could adjust for, and the results are robust. The agency has done their analyses, and for the most part, they find the results are robust, and that's basically where things are.

DR. HAJJEH: But was duration of therapy adjusted for? The duration of therapy, was it adjusted for in the model? It just wasn't clear to me.

DR. KOCH: No, you can't because the factors for adjustment were identified for Protocol 28 and 29. We identified what factors were predictive of response in 28/29. In 28/29, the time period prior to entry was seven days for everybody.

Again, remember time prior to entry is one phenomenon. That's a baseline variable. That's prognostic.

Time after entry is a consequence of whatever therapy you're getting and is basically a correlate, and is a consequence of therapy.

If you had two survival curves in a randomized study and they were different from one another and you adjusted for time of treatment, you'd be adjusting for the outcome you were analyzing, and the treatment effect would disappear in a randomized

study.

So you cannot consider time after study entry as a confounder. It's part of the treatment effect. Time before study entry, yes, there's differences. In the one group it's all seven days. It can't be adjusted for because it's seven days for everybody.

DR. BLACKWELDER: I disagree with you, Gary. I think you can adjust for it, and that's what Dr. Navarro did.

The point about the randomized study, it's a very different type of study. So the same point doesn't apply here because those who entered at seven days in the historical control had a lot more time to die. They had a lot more chance to die before they got to a certain duration of therapy than the ones in 019. They had already survived that long.

DR. KOCH: Yeah, we can try to do some adjustments for the time that preceded study entry, but the time after study entry is basically their duration of follow-up and is a consequence of the treatment they got.

DR. BLACKWELDER: It seems to me that Dr. Navarro's analysis adjusts for the mortality. I mean, I still don't see why it's not okay.

But there's one more analysis I'd like to see, and I think it's the one that Dr. Hajjeh, again, was trying to promote. If you take the subgroup in the 019 who were getting worse and who experienced a 30 percent favorable response according to Dr. Sable and tried -- I'm not sure how well you can do this now -- if you tried to get a subgroup from the historical controls that had the same length of therapy and were at the same point, they were also getting worse, if you had that information or as close as you can get to it and start from there; I would suggest you do that analysis and see how they compare.

I'm not sure if you understand what I'm saying, but both groups would start with the same type of patients and the same underlying diseases and the same duration of therapy, and one continues standard therapy and one is switched to caspofungin.

DR. CHODAKEWITZ: I think it's a point well taken, and I think we have the limitations of the data as was discussed inherent in the historical control study. It is something we can go back and try to do.

I do want to though emphasize because I think your goal is to try to get the most comparable populations possible to do your comparison, but I do

think we have to be careful as we go back and think whether we can do that because they are inherently different populations that were enrolled. We don't have all the data to tease out those kind of subtleties, and so, therefore, I think we also want to look.

Keep in mind the study overall, as well, and remember that those confidence intervals show that there's a lot of things we are not measuring. Perhaps even if the number is lower we still have the inherent strength which we are looking at, which I think is a bias against caspofungin in terms of overall the fact that it's salvage, including the kind of patients you're alluding to versus primary therapy.

We can go back and try to take advantage of our data to tease out a comparable population, and we can go back and do that, but I do want to go back also to the strength of the overall observation as well.

DR. BLACKWELDER: Well, I think what we're suggesting, we're trying to do -- you can't do it perfectly -- but get back to a subgroup who look like the salvage group, right?

DR. HAJJEH: Right, yeah.

DR. BLACKWELDER: Yeah, especially those

who were getting worse already.

DR. HAJJEH: I mean we can probably discuss further later, but I just had a couple of quick questions.

Regarding the criteria for entry into the study, and you're asking for this for the drug labeling, would most clinicians consider seven days after initial therapy as refractory? In their routine management, would it be a point where they usually would think about switching therapies?

And it may be all of the experts on the panel and Dr. Walsh and his group can comment on that.

DR. SABLE: If I could just first briefly comment that the criteria in the study were a minimum of seven days in which patients were showing either progression of disease or failure to respond, and the investigators made those assessments at the bedside, and the data were then reviewed by the expert panel, and the expert panel actually felt that the people -- they were consistent with their determinations of whether patients were refractory or intolerant.

So while the criteria of seven days isn't going to be the same, I think the duration, having the information about progression of disease or failure to respond was at least in this study the way it was

done, was able to be assessed by investigators and confirmed by an expert panel.

ACTING CHAIRMAN GULICK: Others want to ring in? Dr. Graybill.

DR. GRAYBILL: I think that same Slide 41 that Dr. Navarro put together really gives that data very nicely. In the 028 and 029, 206 patients, 132 of them were in the zero to 25 days, and the response rate was 6.8 percent. So you don't have a lot of time to screw around trying to figure out whether your patient is going to get better or not because these people really go down particularly quickly.

So seven days I think probably is about as long as you can wait. Unfortunately X-ray changes don't occur fast, and it is very difficult at times to tell whether a patient is clearly getting better at seven days, but clinicians will get anxious fairly, fairly quickly.

ACTING CHAIRMAN GULICK: Okay. I think this is a good place to stop questions, except for Mark Goldberger.

(Laughter.)

DR. GOLDBERGER: I thought I might give a little clarification now that actually everyone has had a chance to make some comments about, you know,

Question 1 and the issue of safety and efficacy.

If this were, you know, a normal randomized trial against an approved active comparator, then, you know, the expectation from an efficacy perspective is that the experimental drug would be shown to be equivalent, or to use the term in the regulations, "similar" to the approved comparator, and we would have worked out a definition of similarity with the company, and then those analyses would be performed, you know, if there were an issue. And I'll come to some of the other clarifying issues in a second about it. We would have to address it.

Here, of course, the situation is more complex because this is not a randomized comparative trial. The historical controls were put together, you know, after the active arm was already underway, and there were many other issues that we've talked about.

So as a consequence, we have not certainly done any formal statistical analysis because I think either the P value or the confidence interval might give a sense of precision that, you know, was not totally warranted.

And, therefore, at one level we're sort of left to asking your opinion in a subjective way as to whether you think the product is effective, keeping in

mind that the standard is that it should be as good as what the comparator is.

Now, a couple of other clarifying issues. When we make those determinations, and when we look at data, we take into account a couple of other things. One is the patient population. That is to say if the patient population has limited or no other options for therapy, then when we look at how well the experimental arm performed, we'd take that into account.

We might be willing to take a less effective experimental arm if it appears that there's still a group of patients who might benefit.

I will say by means of example in the past, in trials of pneumocystis pneumonia we have approved a couple of products. When compared with standard therapy, they actually showed a worse mortality experience in the clinical trial. Nevertheless, it was well recognized in pneumocystis that there are refractory intolerant patients who could benefit from such therapies. So we would take that into account.

And finally, what we would also take into account is safety profiles of the product. If you've got a product that's marginal compared to approved

therapy and seems to have a worse safety profile, that's, of course, extremely problematic.

As the safety profile gets better relative to the approved therapy, we would also take that into account in, you know, making an approval decision, but it is important to keep in mind that the company has shown the logistic regression analyses that would imply superiority. I think it's important to say that they themselves certainly in the discussions we've had with them have never claimed that.

I think it's interesting to see those analyses in terms of thinking about the robustness of the data, but that's not the standard that's required, nor is there any way we would say in product labeling this is better than what's out there.

It's simply a way of approaching the issue. Is it reasonable to conclude that on balance this product is as good as what's currently available?

And I think that it's important to keep that in mind when you think about what the standard is for approval, not all the other issues with standing in terms of additional studies that may be important prior to approval, after approval, et cetera. In other words, for the population for which the drug is intended.

ACTING CHAIRMAN GULICK: Thanks for that clarification.

I think what I'd like to do is take a ten-minute break and then come back, and we will consider the questions one at a time and have each person on the committee have an opportunity to comment and then take a vote.

(Whereupon, the foregoing matter went off the record at 3:27 p.m. and went back on the record at 3:40 p.m.)

ACTING CHAIRMAN GULICK: Okay. Welcome back, in the home stretch here.

So we're going to consider the questions to the committee starting with Question No. 1. Did the data presented demonstrate that Cancidas is safe and effective for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of standard antifungal therapy.

I'd like each committee member to comment, and we'll start with our expert consultants starting with Dr. Schapiro.

DR. SCHAPIRO: So to answer the first question, actually to relate to the three subquestions posed by Dr. Goldberger, I think the amount of safety data considering this indication is sufficient. I

think in this patient population that is so sick and has such advanced disease with such mortality, I think the safety data for that indication is sufficient.

I think regarding the population that we're looking at, once again, I think regarding refractory patients I think we've heard input here also, and I think from our experience as clinicians, you do not wait long. So I do think that this would be somewhat representative of a refractory population.

I think regarding intolerant, we should keep in mind that there's a very, very small N of patients here that were actually looked at, and although we categorize those as refractory or intolerant, this study really looked at refractory patients, and it was really two different populations, one being large and one being small.

When you try to delineate each of those, I think the intolerant group is really too small to evaluate, and it seemed like those had quite favorable outcomes, and it was really two different studies looking at those.

Regarding the historical control, I would like to say that I think that both the work done by the group at Merck and also the FDA group should be commended for an outstanding, very in depth

statistical analysis of this. I think great efforts were made here to tease everything that could be out of the data, but I do think that the comments we heard from Dr. Blackwelder, Dr. Wong, Dr. Hajjeh, and Dr. Mathews are relevant.

Going back to what Dr. Goldberger said, as a gestalt, it gives us something, but for that to really be meaningful as a comparator, it's very difficult. I think if we would have asked the three colleagues on my right is 40 percent response good, they would have said that's probably the best you can do with the other things. That's about what I feel about the historical control.

I don't think it's really pseudo data. Either it's data or it's not. I think from the comments we heard from some of the panel I'm not sure how much that really helps us. I do think that we should still strive to do comparative studies, and although I understand the difficulties, we should also recognize, I think, based on today what difficulty there are with historical controls despite -- and again, I would say the work done here by both groups was outstanding -- we're still left with a lot of open questions.

So I think that for this indication we do

have enough safety data for these patients, I think, that they've defined as refractory patients, and as far as efficacy, the historical controls do not add much, but I think from the expert consensus it seems like this is as best as we are doing with what we have today.

What I would say though is we have a problem that we're looking at patients who had an intervention versus patients who did not have an intervention. The patients at seven days in this study were enrolled in a trial and began getting therapy, and the other ones were arbitrarily on a certain date considered to be enrolled.

That model somehow is also an inherent difficulty here, that we have to always remember that a patient who is now being looked after as part of a study and is getting a new therapy, it's very difficult to arbitrarily just take the other patients and say from here.

So I think the historical control, despite all of the efforts, does not give a lot of information, and I would say that we were more basing this on just a consensus of how poorly those patients do.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Stevens.

DR. STEVENS: Well, in terms of the more safety data that we'd like to see, I have already made a point about like to see some more preclinical data that I think would be easy to get and directly test the question of co-toxicity with steroids, which is a clinically relevant question, and we don't have to go back and tease out past experiments that were done. I think it's easy enough to do. So I've made my case about that.

As far as the efficacy data, I think we're really confounded. I think Brian Wong said it as well as anybody, which is that the historical control data is just very difficult to evaluate in comparison.

You know, having said that, I think Merck has done the best that they can, and there's a line about don't let the perfect stand in the way of the good. I mean this is about as good as it can get, and they did a very diligent job of trying to tease out what they could.

But Brian's comments notwithstanding, it's still problematic to assess where this drug exactly stands.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Graybill.

DR. GRAYBILL: In terms of the doses, duration, safety data, my biggest concern is just exactly what's been said by Dr. Perfect. A lot of the patients here are going to be getting cyclosporin. This is who these transplant patients are who get aspergillosis.

Tacrolimus, it looks fine, but tacrolimus is a lot more expensive than cyclosporin. Cyclosporin is a more popular drug. Therefore, it behooves Merck to accumulate more data on cyclosporin.

They are now conducting a series of studies on candida, randomized empiric therapy trials, et cetera. I would hope that they would include patients with cyclosporin in those studies. I would hope that they would not offer the out to an investigator to switch to tacrolimus or any other thing, just to say if you're going to treat them, put them in, and if you're not, then you can decide on the basis of the safety data that Merck has whether you think that's too big a risk or not to put them in.

But I think we need that data, and we've already talked about the maximal doses and so forth and how we need that, and I think that Merck is in agreement on that.

The treatment -- another place that the

difference that we had on the historical control and on our 019 study was that there were very few people who were intolerant who were in that historic control. Almost all of them were refractory patients. Yet another reason to say this is a different population.

I would be much more interested in seeing how people do ultimately in refractory patient disease. That's where the physicians struggle immensely, and I would just presume that they'll do better if they're intolerant to other drugs, that you'll show a better effect.

The historical control studies, I've already brow beaten a couple of people at the FDA to suggest that the high fees that you charge these drug companies to do this evaluation well some of that money could be sent to the CDC or to another neutral group to have them generate an ongoing, rolling, continuous entry database to acquire the information that one would need so that the folks at Merck would not have to struggle so much in the future or other companies, and that we could have a database that everybody would accept and go through all of the things that we've been fighting about this control group that has been so difficult to deal with.

And I think that's a soluble problem,

maybe not for Merck now and not for the guys who are already in for the next drug, but I think that's something that we very much need to address, and I would use my taxpayer's dollars to do that.

ACTING CHAIRMAN GULICK: Dr. Perfect, not standing in the way of Dr. Good.

(Laughter.)

DR. PERFECT: Definitely not. I don't think so.

I made my point on toxicity issues. Actually it seems like this drug is very, very safe and really has a lot of advantages because of that, including its drug interaction issues.

It's kind of ironic that cyclosporin sits out there and the fact that really this is probably going to be one of the big advantages of this drug, is its safety profile.

You know, we can go over and over the issues of historical controls. We can go over the issues of the study that was done simply because it had to be done.

I bring up one more point. Someone asked the issue of reference points. This thing is a moving target. It continues to move. The treatments move, and where we're at today was not 1995 even.

And in my talk I tried to give some review of what I know from the data that's been published mostly in abstract, and if you put the issue, I don't want to beat to death the 40 percent rule because I suspect it won't stand up to statistical analysis and may not even be real, but if you take all of the other types of studies that have been reported in this type of intolerant and the refractory type patients, including lipid products that are continuing to look on, you see a similar type of response rate.

Now, again, there's a lot of different issues there, apples and oranges, intolerant versus refractory, what's the endpoints in these studies and stuff like that, but it's interesting that it comes around to that area. This drug is in that area of what happens when even the newer drugs are exploited and used.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Fletcher.

DR. FLETCHER: Like the other comments that have been made, I think the uncertainties here are high both in terms of safety and in terms of efficacy.

With regard to safety first, the safety profile, I think, does look acceptable. However, this

is a new class of drugs, first of a new class to be approved, and the duration of therapy in patients has been quite limited.

So, you know, there is, I think, real uncertainty about what is the safety going to be in the real world for durations of treatment that are longer than what we presently have data for.

However, I think when you compare it with the drugs that are available, I do believe it does meet a safety criterion.

On the efficacy side, again, it's the uncertainty with the small amount of data that are available and the lack of a controlled group. Under a criterion of should be as good as, I think I would, you know, come to the opinion that, yes, it probably meets that criterion of should be as good as, but I have much more uncertainty about that efficacy criterion than I do the safety one.

A few additional comments on the sub-questions. Clearly, more information needs to be obtained on the dose of the drug and the duration of therapy.

In terms of the patient population, the restriction to refractory and intolerant, that certainly seems to be appropriate for the way the

study was designed.

I at least believe that, you know, the purpose of a package insert, however, is to communicate what we know about this compound and using it to patients as well as physicians, and I think the agency and the sponsor need to find some way to point out the lack of successes in the persistently neutropenic patients and the even worse results in treating patients with CNS disease.

Just to make a point about, you know, that Dr. Perfect made about black boxes, a person can leave that up to the agency. Where do you need a black box and, you know, where you don't, I'm must more interested in communicating, you know, what we know and to the point on the drug interactions, again, while some comment may need to be made about not using cyclosporin and caspofungin together, I still believe that what we do know about using those drugs together in some way needs to be communicated.

With regard to the historical control, the limitations of this have already been discussed. I don't have anything, you know, new to add, but I certainly would think it would be worth some collective effort on the part of industry and the agency, you know, to really look at this type of a

study design.

I suspect other panel members are going to comment about this, and I know we'll come to it later, but it does contribute to and, in fact, because of these uncertainties that we have particularly with regard to the efficacy of the drug.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Mathews.

DR. MATHEWS: I'll be brief. I think that the analyses convinced me that it's certainly as good as whatever treatments the historical control group got.

Duration of therapy is a question mark in my mind. I don't think we really saw enough data to be able to say what should be the trigger to switch to some kind of maintenance or therapy, you know, as a resolution of fever. Is it complete radiographic regression? Is it, you know, resolution of the underlying immunosuppression or whatever?

And with amphotericin B, many people use so many grams or sort of an arbitrary endpoint for duration. So I think that needs to be studied more, and I think the other points have already been made.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Hajjeh.

DR. HAJJEH: Yes. I think also that the data presented today did show that the drug is efficacious. I think it's hard for me as an epidemiologist to get over the small numbers we're talking about here. We're basically talking about an N of 28 responses total, but I think the 19 data is quite convincing that the drug is working in a subgroup of patients.

It would be helpful to try to characterize more this group where it really worked, the 28 or so where it worked, and try to detect predictors of good response versus predictors of failers, like they've tried to do in the historical trial.

The same concerns regarding the doses. Probably higher doses would be more effective, but actually I meant to ask this question before. There were two cases who developed CNS aspergillosis while on treatment, and I was wondering, you know, whether these two patients, in particular, present some subgroup so we could anticipate that complication.

I think restricting the drug to refractory and intolerant patients is feasible. The historical control was okay, and we mentioned all the point. I think the analysis or the study can benefit from further analyses, and other things can be controlled

for.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Stanley.

DR. STANLEY: Well, I think most of what I think has already been said by somebody, but just briefly to recap, I think from the study that we've seen, from 019, it does appear to be efficacious and safe in this particular population of patients.

I'm very uncomfortable with the number of folks that we've seen that have been on long-term treatment with this, and I think that's something that really needs to be looked at, and those data need to be collected down the road.

I don't see any evidence that there's been a good look even in an animal model at tissue accumulation of this drug long term, and I think that's something that I'd be concerned about if we're looking at other uses of this drug down the road.

For right now in this particular desperate population of patients, I think that the Study 19 shows efficacy and safety. I think that the restriction must be on this population of refractory and intolerant patients, and as far as the historic control, I personally found that study fairly unuseful.

I mean, if I just look at 19 alone and see that kind of a response in this population of patients, that's probably enough to convince me, and the historical controls study is just so hard to interpret.

ACTING CHAIRMAN GULICK: Thanks.

Dr. Wong.

DR. WONG: I guess let me begin by saying I think that, you know, I'm very glad to see this drug brought forward, and I think it's an important addition, and I also want to say that I found the presentations by the sponsor today to be really first rate. I thought that, you know, you brought your data in and analyzed it honestly and presented it forthrightly and answered questions in a way or with a level of candor that we don't always see here. So I want to commend you.

I think that the data suggest very strongly to me that the drug is effective in aspergillosis, but they don't prove it because we don't have contemporaneous controls. That's not to say that -- you know, I think I certainly will vote, you know, to recommend approval, but I think that, you know, the case has not been proven.

Amount of safety data looks good. I agree

that longer durations and higher doses need to be looked at.

The restrictions on the population, I think, are appropriate. I'm a little surprised actually that the first time we've ever seen data on this drug on the first representative of a completely new class is for this sort of an indication in this sort of a population. It would have been much easier for me to evaluate the results from the candida trials, and you know, I imagine those results will be forthcoming in not too long and, you know, would have been much easier to make decisions.

But, you know, for this population this makes sense, and I agree with Sharilyn that, you know, although the historical control study, I think, was very well done, it didn't convince me in any way that this drug was more effective than just knowing that the overall response rate was 40 percent in this population.

ACTING CHAIRMAN GULICK: Dr. Kumar.

DR. KUMAR: Recognizing the inherent difficulties of doing the protocol in patients with invasive aspergillosis, with the data that was presented today both by Merck and by the FDA, I'm comfortable in saying that the safety data that is

presented is acceptable, and though the efficacy in my mind is not proven, my gut sense is that it's as good as what we currently have available.

ACTING CHAIRMAN GULICK: Thanks.

And Dr. Blackwelder.

DR. BLACKWELDER: With regard to safety, I agree that the data shown so far do support safety, that it's safe, and would suggest the additional data that I think three people have asked for.

The point was also made that the numbers are very small for intolerant patients, and so I would suggest further studies in that group even though the response rate was pretty high, and with regard to historical control study, we've spent most of our time on that, it seems, and I would like to see some additional analysis or see it done, not that I necessarily need to see it, but the kind of analysis that Dr. Hajjeh and I have suggested.

In my opinion, it's not clear that efficacy has been shown, but if I step back and think, well, is giving caspofungin better than stopping therapy and giving nothing, then I don't know, but my guess is that it must be, and that's about as far as I can go.

And the problems are not with the

presentation which has been made, which I agree has been excellent. It's with the study design, and I would urge that every effort be made in the future to consider randomized control studies, and if they're impossible, you can't do them, but if they're difficult, then with enough effort you can.

ACTING CHAIRMAN GULICK: So if I can summarize the committee's thoughts, people recognize this is a new class of antifungals with a novel mechanism of action. The indication is a disease with high mortality rates, given our present medication set. It's a patient population which is critically ill and has few options, and that swayed many of the committee's opinions on the data that was saw presented today.

In terms of safety, most people felt that this was an acceptable amount of information for this patient population, although people wanted to see data on higher doses of the drug, and perhaps that could be a Phase IV commitment.

Also, people noted that we have relatively little data after 28 days and relatively few numbers of patients, and that probably should be another Phase IV commitment.

People pointed out the cyclosporin

interaction, and in addition, it was brought up over the course of the day, other patient populations.

In terms of efficacy, I think we heard the same theme sounded. People had a gestalt, a gut feeling that this was as good as our therapies now. Several people pointed out perhaps we don't have it proven, but highly suggestive of the data in small numbers that we saw.

Let's see. The historical control. People felt that the information was interesting and well presented, but questioned whether it really added information to our evaluations today because of the biases, because of the difficult to interpret data, and there were several calls for comparative studies in this field, although as we heard earlier that's problematic.

One other area of Phase IV commitments that was brought up earlier today was synergy with other antiretroviral agents just because of the recognition that this drug will likely be used in combination with the other agents.

Okay. I'd like to take a formal vote at this point. Just for clarification, our experts are here to advise us, and their votes are nonbinding, but I would like to give you the opportunity to vote

either approve or disapprove, and we'll go one by one. So you can decline or you can vote.

And, again, this is more for the interest of the committee than anything else.

DR. SCHAPIRO: I would approve.

DR. STEVENS: Same

DR. GRAYBILL: Same.

DR. PERFECT: Same.

ACTING CHAIRMAN GULICK: Okay, and now we'll take the formal votes. There are eight committee members represented today.

Dr. Fletcher?

DR. FLETCHER: I would vote to approve.

ACTING CHAIRMAN GULICK: Dr. Mathews.

DR. MATHEWS: Approve.

DR. HAJJEH: Approve.

DR. STANLEY: Approve.

DR. WONG: Approve.

DR. KUMAR: Approve.

DR. BLACKWELDER: Approve.

ACTING CHAIRMAN GULICK: And I as Chair also approve.

So the count is eight for approval and none for disapproval.

Let's take a deep breath there.

(Laughter.)

ACTING CHAIRMAN GULICK: Okay. The second and third question, we can be a bit more informal on our consideration, but we're really looking to give advice both to the agency themselves and to the sponsor. So I don't think we need to go around the table like we just did, but let's have people chime in.

Many of these issues we've talked about this morning and this afternoon. So Question No. 2, we just recommended for approval an indication for patients refractory to or intolerant of. However, what additional information, preclinical or clinical, would be needed to support the indication of initial therapy or first line treatment of invasive aspergillosis?

Dr. Schapiro?

DR. SCHAPIRO: So, Trip, to maybe look at two and three a little bit together.

ACTING CHAIRMAN GULICK: Sure.

DR. SCHAPIRO: First of all, I do think we have to get the dose down for this agent. To remember what we said in the beginning, fungal infections are serious infections with high mortality. We have here a compound which looks very safe, and I think we have

to work out the dose.

I think some of the things we should keep in mind and something that can be problematic -- and I think here this was one of the problems -- that we have standard ways of doing sort of the animal models. We look at, you know, how many animals are still alive, how long they're alive, and if there's not a high mortality in those animals, we start getting good results at relatively low doses, and we don't really work out higher doses.

We may have to be more creative. We may have to look at tissue clearance in these animals; make more difficult criteria where we can tease out an effect of higher doses.

If I'm not mistaken, with this compound a lethal of dose of 20 to 40 times some of the doses that were being given in animals. Therefore, it looks like we had a long way to go. I think the company did a good job with the standard criteria, but we were finding, you know, 90 percent success. So basically you were done.

Looking at more strict criteria like, again, clearance of organisms from some of the internal organs might have been a more sensible way of looking at higher doses, and I think, again, taking

that into human studies we'd be able to look, again, at giving much higher doses, and I think that's what we might find.

So I think dose ranging is something which we would definitely need. Again, I would look at more creative ways in the animals and, once again, in humans I think we have to do that. And that would also help us possibly with the safety since the safety data was a little bit patched together. I'm sure we're going to find that when we want to go to higher levels that we're actually starting anew.

Had we a little more information from the animal models that we're still getting benefit by increasing the doses, we might have done more work in humans, and once again, to accept that aspergillosis is different than candida, we would realize we probably need to go higher.

I think one thing that I would like to do again, I think we should use the opportunity if we have tissues at the end of the study. I think the post mortems in these patients -- that tissue is very precious. I think we learn a lot from looking at tissue in patients that fail.

Looking at resistance will be a key issue, I think. To understand success, we have to understand

failure.

I think going back to Dr. Perfect's opening talk, this rule of 40, obviously 60 percent of patients are still failing. Why are they failing? Is it because they're so sick? Is there not enough drug getting to the bug, or is the bug resistant?

And I think some of those we would find if we did again more studies looking at the patients who were actually failing to understand why they're failing.

ACTING CHAIRMAN GULICK: Dr. Stanley.

DR. STANLEY: I think to use this as a first line drug you're going to have to clarify or answer the question of whether it's fungicidal in aspergillus, and that hasn't been able to be answered because of the limitations of that science.

But I would want to have more work in that area and have a better clarity for its effects on whether it's static or cidal (phonetic).

DR. GRAYBILL: Could I just pick a little politely ever so much a bone with you, Dr. Stanley?

DR. STANLEY: Sure.

DR. GRAYBILL: I don't think we have any drug that's fungicidal in vivo, not a one. All of the definitions we use are test tube definitions. We have

used fungicidal amphotericin B in AIDS patients with Streptococcal meningitis, histoplasmosis, coccic- whatever. You stop it; they relapse and it comes back.

So I'm much more interested in what happens in the in vivo situation than what happens in the test tube, and I don't think anything is fungicidal really.

DR. STANLEY: Well, and I would certainly bow to the mycologists in the group since I'm not one, but given that, the other question that I had down that I would want to know more about before making it a first line drug would be the duration of therapy.

I mean, we've talked about the dose. What is the appropriate dose? What is the appropriate duration? And what's your readout? And then how do you monitor after you stop there?

And then the last thing is to continue a vigilant search for resistance and what the mechanism would be or whether it does develop. I mean, we do understand a lot about at least one mechanism apparently, and I was happy to hear that, but I think we would need vigilance and continue to look for that if we're going to use this as first line.

ACTING CHAIRMAN GULICK: Dr. Mathews?

DR. MATHEWS: Well, you know, I think that the availability of this drug now should make it more feasible to do a randomized controlled trial as a first therapy, probably comparing it to one of the liposomal preparations so that the limiting toxicity issue of amphotericin B doesn't limit the adequate comparison of the two agents.

You know, it's going to be very difficult, but I think if the data similar to what we've seen today is really looked at by clinicians, I for one would not feel that I was compromising a patient by allowing them to be randomized either to this drug or to one of the amphotericin preparations initially.

ACTING CHAIRMAN GULICK: So you feel you have equipoise about the two therapies at this stage?

DR. MATHEWS: Yes, I do agree with Dr. Schapiro's point of it, that the dose should be the right dose, and so that probably the dose escalation studies need to be done first before you take it into a randomized trial.

ACTING CHAIRMAN GULICK: Dr. Wong.

DR. WONG: I agree with that. I think that we've now arrived at a point that before this drug is considered approvable for primary therapy, it should be shown to be equivalent to a standard

therapy.

So I think that requires a formal prospective comparative trial, and it could be done by comparing it to amphotericin B, and some sort of a dose response or, you know, dose escalation design within the trial might be useful as well if you didn't want to do that in advance.

Just to quickly go on to the third question, the role of animal models I think is supportive. Whether a drug is fungicidal or fungistatic means nothing to me. I think it is irrelevant.

Microbiological endpoints as compared to clinical endpoints, I think both are useful, but clinical endpoints are primary, and I hope in my remaining time on this panel not to have to struggle with anymore analyses of historical control groups.

(Laughter.)

DR. GRAYBILL: But you will.

ACTING CHAIRMAN GULICK: Dr. Graybill.

DR. GRAYBILL: You're going to be out of luck, Dr. Wong, because that's what you're going to get is more of those.

I would love to see this drug looked at for primary therapy. I think the FDA will have to

rethink how it does its studies. You're not going to get 300 patients or 200 patients or 150 patients with documented aspergillosis by current criteria in each arm. It just ain't going to happen.

There may be some alternatives in the near future that would let us do that. One would be or is the development now of including radiographic lesions specifically in the diagnosis, these so-called LISAs. There was a nice article in Clinical Infectious Diseases about that, and one of the things that they found is that when they resected the lesions, many of which did not show a hard diagnosis of aspergillosis beforehand, but they suspected it, and they resected the lesions, and 35 out of 39 patients had aspergillosis confirmed at biopsy. That was hard diagnosis, and they did well.

So using X-rays is one thing, and also putting in, as the Europeans and Americans are doing now -- Drs. Patterson and Walsh, I think, are on the committee to do this -- is building in seroconversion. I think it's just so important that we get this ELISA test developed and licensed so that we can look at it.

There are a number of people who think this is very good. It would allow us to get the people earlier, and we may be able to get to a large

number of populations earlier and get to a lot of people before they're sort of in a desperate strait and increase our numbers.

So what is the primary therapy that you would compare it with? The only one that we really have is amphotericin B, and that's a nonstarter. So the FDA is going to have to rethink what it's going to allow as primary therapy, and I think your suggestion of AmBisome is an excellent one. With the reduced toxicity, with certainly a large historical use of Ambisome, I think it's a very reasonable drug to go with, and it's probably one that physicians would select between.

The other thing I would think about would be good would be, I guess -- I don't know if Merck wants to hear this -- but combination therapies is something we really haven't addressed much, except a little bit of talking about it in animals. This disease is so bad that a lot of physicians are going to be thinking about combination therapy.

There is a fair amount of animal data, not all of it published, some of it presented as recently as ICAAC, which shows either additive or neutral effects. There's nothing that shows really antagonism.

So all of the arguments about triazoles and so forth, this drug looks good with triazoles. It looks good in animals with amphotericin B, as well. So those are possibilities.

And I guess going to Item 3, that's a place where animal models would be useful to further increase that.

The impact of whether it kills an organism, I've already given my opinion on that.

The relative importance of microbiologic endpoints compared to clinical endpoints. I think clinical endpoints are key, but I think as long as we use the clearest endpoint, which is death, we're going to have a harder time, a more complete response radiographically.

I mean that's a lot to ask for in most of the patients here where partial response is not complete responses.

There was another provocative thing, again, using the antigen. I'm not pushing my own thing because I'm not working with the antigen. This is not personal experience, but there was a lovely paper at the ICAAC this year which suggested that within a very short period of time after starting therapy for aspergillus using the ELISA antigen, the

sanofi test, that they could predict whether the patient was going to life or whether he was going to die.

And that suggest that we might be able to use this in the same way that we use histoplasma antigens and cryptococcal antigens, and perhaps we can use that or difference in response rates for antigens. We can't do liver biopsies on these people serially, but we might be able to get an idea of fungal load, and we might be able to do a comparative trial using that and looking at the differences in continuous variables to hopefully use smaller numbers of patients in a Phase III trial if we're able to do that kind of thing, or quantitative PCRs might be another possibility and a way to go.

But I think we need to redesign our studies. We'll never get a classic Phase III trial.

Thank you.

ACTING CHAIRMAN GULICK: Dr. Kumar.

DR. KUMAR: I'd like to make a comment regarding Question 3, and it's mainly more of a plea than an advice to either the sponsors or the FDA regarding the therapy of patients with refractory or intolerant aspergillosis.

And picking up on what Dr. Graybill just